8 50. (New) An isolated polynucleotide that encodes a polypeptide capable of dephosphorylating an activated MAP-kinase, said polynucleotide comprising a sequence at least 80% identical to a polynucleotide that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2.

9 51. (New) An isolated polynucleotide that encodes a polypeptide capable of dephosphorylating an activated MAP-kinase, said polynucleotide comprising a sequence at least 90% identical to a polynucleotide that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2.

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10 52. (New) The isolated polynucleotide of either claim 8 50 or claim 9 51, wherein the polypeptide that is capable of dephosphorylating an activated MAP-kinase comprises aspartic acid at position 119 of SEQ ID NO:2 and VHCNAGVSRAAAIV (SEQ ID NO:3) at positions 148 through 161 of SEQ ID NO:2.

REMARKS

Reconsideration of the present application in view of the above amendments and the following remarks is respectfully requested. Claims 2-14 and 22-25 are currently under examination. Applicants hereby cancel claims 3-5 without prejudice to the filing of any divisional, continuation, or continuation-in-part application. Claim 11 stands allowed and has been amended to more particularly point out and distinctly claim subject matter which Applicants regard as the invention. Claims 2, 6, 8, 10-12, 14 and 22 have been amended and new claims 50-52 have been added to more clearly define the subject matter encompassed by Applicants' invention. Support for the amended and new claims may be found in the specification, for example, at page 8, lines 6-17, and at page 9, line 26 through page 10, line 24. The specification has also been amended solely to correct typographical errors. No new subject matter has been added.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made.**"

OBJECTION TO THE SPECIFICATION

In the Office Action received from the U.S. Patent and Trademark Office (hereinafter "PTO"), the PTO objects to the specification for informalities on page 12 and page 44 of the present application. Applicants thank the Examiner for pointing out the unintended inconsistencies between the specification and the Sequence Listing, which are the results of typographical errors. According to the amendment submitted herewith, the specification has been corrected in a manner suggested by the PTO. Applicants therefore submit that the amendment obviates the basis for the objection and respectfully request that the objection to the specification be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claims 6, 14, and 22-24 stand rejected under 35 U.S.C. § 112, second paragraph, for indefiniteness. Specifically, the PTO asserts that claim 6 is confusing in that it refers to non-elected claim 1. The PTO is also unclear as to the meaning of "DSP" in claims 14 and 22-24, asserting that the meaning of this acronym should be recited in the claims. In addition, the PTO alleges that in claim 22, the recitation "antisense polynucleotide according to claim 10 or claim 11" is indefinite, asserting that the subject matter of claim 11, an isolated polynucleotide, lacks antecedent basis for an antisense polynucleotide. The PTO further alleges that claim 22 is confusing and incorrect in its recitation of a "method for detecting DSP-4 expression . . . comprising . . . detecting an amount of DSP-4 polynucleotide that hybridizes to the antisense polynucleotide . . .". Specifically, the PTO asserts that expression is not measured by the presence of a polynucleotide, but is instead determined by transcription and translation of this polynucleotide into protein.

Applicants respectfully traverse these rejections. With respect to claim 6, Applicants submit that the amendment submitted herewith removes the reference to non-elected

claim 1, thus obviating the basis for this rejection. Applicants respectfully request that the rejection of claim 6 be withdrawn.

Applicants respectfully traverse the rejections of claims 14 and 22-24 and submit that when read in the light of the present specification that defines DSP-4 as a dual specificity phosphatase (*e.g.*, specification, page 12, lines 11-14), the recitation "DSP-4" in the claims clearly points out and distinctly claims the subject matter of the invention. Nevertheless, solely to expedite prosecution, and to make explicit what was implicit, Applicants have amended claims 14 and 22-24 to recite "dual specificity phosphatase-4." Accordingly, Applicants respectfully submit that amended claims 14 and 22-24 fulfill the requirements of 35 U.S.C. § 112, second paragraph, and request that the rejections of theses claims be withdrawn.

Turning to claim 22, Applicants respectfully submit that as amended herewith, this claim employs proper antecedent basis, and that there is no lack of clarity regarding what is the meaning of "expression." The subject matter of claim 22 is defined with a reasonable degree of particularity and distinctness, such that a person skilled in the art, given the disclosure in the present application, would be apprised of the scope of the claim.

As conceded by the PTO and as known to persons skilled in the molecular biology art, polypeptide expression includes the step of transcribing DNA encoding a polypeptide into mRNA, followed by the step of translating the mRNA into a protein product (*i.e.*, polypeptide). Applicants submit that it is well accepted in the art for skilled artisans to detect and/or quantify levels of a particular mRNA species (*i.e.*, a transcription product) that encodes a particular polypeptide, in order to determine whether a particular gene is transcribed; furthermore, it is commonplace in the art to refer to this step as determination of "expression" of such an mRNA. For example, the instant specification teaches that by combining a labeled nucleic acid probe with poly A+ RNA from human tissues under hybridization conditions, a person skilled in the art can determine whether DSP-4-encoding mRNA is "expressed" in human tissues (*see* specification, page 45, Example 2). Applicants submit that a person skilled in the art would readily appreciate that Applicants' disclosure of a method for detecting such polynucleotide levels is a measure of DSP-4-encoding polynucleotide expression, where it is known in the art to refer to "expression" of a particular mRNA (*see, e.g.*, Muda et al., *J. Biol.*

Chem. 272:5141-51 (1997), a copy of which is enclosed for the Examiner's convenience, at page 5146, Figure 8 (Expression of MKP-4 mRNA in human tissues)).

In view of the present amendment and the above remarks, Applicants submit that the present claims comply with the requirements of 35 U.S.C. § 112, second paragraph. Applicants therefore request that the rejections of these claims be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 2-5 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Specifically, the PTO alleges that the claims encompass polynucleotides from unrelated genes that encode polypeptides having 10 or 15 consecutive amino acids of SEQ ID NO:2, and further asserts that the instant specification does not teach a person skilled in the art how to make and use such polynucleotides.

Applicants respectfully traverse these rejections for lack of enablement and submit that they are rendered moot by the present amendment. In view of the cancellation of claims 3-5, Applicants request that the rejections of these claims be withdrawn. Applicants further submit that, with regard to claim 2, the instant specification (*e.g.*, at pages 9-12; pages 43-45; and in the Drawings and Sequence Listing) provides explicit guidance enabling a person skilled in the art to make and use the claimed isolated polynucleotide encoding a polypeptide having the amino acid sequence set forth in SEQ ID NO:2, readily and without undue experimentation. Applicants therefore respectfully submit that the present application satisfies all requirements of 35 U.S.C. § 112, first paragraph.

REJECTION UNDER 35 U.S.C. § 102

Claim 2 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Marra et al., GenBank Accession No. AA000276, and by Marra et al., GenBank Accession No. AA216840. More specifically, the PTO asserts that each reference teaches a polynucleotide that encodes at least ten consecutive amino acids of SEQ ID NO:2. Claims 2 and 3 stand rejected under 35 U.S.C. § 102 as allegedly anticipated by Hillier et al., GenBank Accession No. AA442636, and by Strausberg, GenBank Accession No. AI031656. In particular, the PTO

alleges that each reference teaches a polynucleotide that encodes at least fifteen consecutive amino acids of SEQ ID NO:2.

Applicants traverse these rejections and submit that they are inapposite in view of the present amendment to claim 2, and the cancellation of claim 3. Applicants further respectfully submit that the cited references fail to anticipate the subject matter encompassed by the claims submitted herewith by amendment. The present invention is directed to an isolated polynucleotide that encodes a polypeptide having a sequence as set forth in SEQ ID NO:2. By contrast, AA000276 (Marra et al., reference U) fails to teach or suggest a polynucleotide that encodes the sequence of seven amino acids at the amino terminus of SEQ ID NO:2, and also fails to teach or suggest a polynucleotide that encodes the twenty-seven residues at the carboxyl terminal end of SEQ ID NO:2. Furthermore, comparison of SEQ ID NO:2 with a deduced translation product of AA000276 indicates that the polynucleotide sequence disclosed in AA000276 would encode a polypeptide having at least 28 additional (*i.e.*, non-terminal region) amino acid differences from the polypeptide sequence set forth in SEQ ID NO:2 of the present application. Therefore, Applicants submit that the polynucleotide sequence disclosed in the cited reference fails to meet the limitations of the presently claimed subject matter, where AA000276 at best encodes a polypeptide that differs from SEQ ID NO:2 at nearly 30% of the amino acid residues in that sequence.

AA216840 (Marra et al., reference W) also fails to teach or suggest a polynucleotide sequence that encodes a polypeptide having the amino acid sequence set forth in SEQ ID NO:2. AA216840 discloses a polynucleotide encoding a polypeptide that would lack the 20 amino acids present at the carboxyl end of SEQ ID NO:2, and that would have eight additional amino acids at the amino terminus of SEQ ID NO:2, which eight amino acids are not present in SEQ ID NO:2. Moreover, comparison of SEQ ID NO:2 with a deduced translation product of AA216840 indicates that the polynucleotide sequence disclosed in AA216840 would encode a polypeptide having at least 33 additional (*i.e.*, non-terminal region) amino acid differences from the polypeptide sequence set forth in SEQ ID NO:2 of the present application. Therefore, Applicants submit that the polynucleotide sequence disclosed in the cited reference fails to meet the limitations of the presently claimed subject matter, where AA216840 at best

encodes a polypeptide that differs from SEQ ID NO:2 at approximately 30% of the amino acid residues in that sequence.

For similar reasons, the EST sequences disclosed in AA442636 (Hillier et al.) and AI031656 (Strausberg et al.) also fail to teach or suggest the presently claimed invention. AA442636 merely teaches a polynucleotide that would encode a polypeptide having only 61 amino acids at sequence positions in common with amino acids in SEQ ID NO:2, but AA442636 fails to teach or in any way contemplate a polynucleotide sequence that encodes the amino acids at positions 62-217 of SEQ ID NO:2. AI031656 discloses a polynucleotide that would encode a polypeptide having only 86 amino acids at sequence positions in common with amino acids in SEQ ID NO:2, but AI031656 fails to teach or suggest a polynucleotide sequence that encodes amino acids 1-130 of SEQ ID NO:2.

Accordingly, Applicants respectfully submit that the subject matter of the instant claims is distinguishably novel over the cited references, in compliance with the requirements of 35 U.S.C. § 102. Withdrawal of the rejection is therefore requested.

REJECTION UNDER 35 U.S.C. § 103

The PTO rejects claims 4 and 5 under 35 U.S.C. § 103 for alleged obviousness over Marra et al. (GenBank Accession No. AA000276), Marra et al. (GenBank Accession No. AA216840), Hillier et al. (GenBank Accession No. AA442636), or Strausberg (GenBank Accession No. AI031656). In particular, the PTO asserts that a person having ordinary skill in the art would have been motivated to study the proteins produced by each cited polynucleotide, and would have found it obvious to do so by placing the polynucleotides into a vector and the vector into a host cell.

Applicants respectfully submit that in view of the cancellation of claims 4 and 5 according to the amendment submitted herewith, the basis for the rejection under 35 U.S.C. §103 is obviated, and the rejection is rendered moot. Applicants further submit that the cited references, alone or in combination, fail to teach or suggest the subject matter of the amended and newly added claims. Moreover, Applicants submit that absolutely no teaching, suggestion or motivation can be found in the prior art to combine or modify any teachings of the prior art to arrive at the presently claimed subject matter. Absent the disclosure of the present application, a

person having ordinary skill in the art could not have reasonably expected successfully to achieve Applicants' invention.

Applicants therefore respectfully submit that the claimed invention is nonobvious as required under 35 U.S.C. § 103, and request that the rejection be withdrawn.

OBJECTION TO THE CLAIMS

The PTO objects to claims 7-10, 12, 13, and 25 as being dependent upon a rejected base claim.

Applicants respectfully submit that in view of the present amendment and the above remarks, all currently pending claims meet the requirements for patentability. Applicants submit therefore that the objection to claims 7-10, 12, 13, and 25 has been obviated, and respectfully request that the objection to the claims be withdrawn.

Applicants respectfully submit that all claims remaining in the application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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SDR:MJR
sd
Enclosures:
Postcard
Petition for Extension of Time
Copy of Muda et al., *J. Biol. Chem.* 272:5141-51 (1997)

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Paragraph beginning at line 4 of page 12, specifically lines 6 and 7, has been amended as follows:

A cDNA sequence encoding DSP-4 is provided in Figure 1 (SEQ ID NO:1), and the predicted amino acid sequence is provided in Figure 2 (SEQ ID NO:2). The DSP-4 active site VHCNAGVSRAAAIV (SEQ ID NO:3), is ~~encoded by nucleotide bases~~ located at ~~nucleotide~~ positions 148 through 161 of SEQ ID NO:~~1~~2. Sequence information immediately adjacent to this site was used to design 5' and 3' RACE reactions with human skeletal muscle cDNA to identify a 651 base pair cDNA that may be expressed by a variety of cell types, including heart, testis, thymus and skeletal muscle tissues. This cDNA encodes a protein of 217 amino acids that is referred to herein as dual specificity phosphatase-4, or DSP-4. DSP-4 shows significant homology to other MAP-kinase phosphatases, as shown by the sequence comparison presented in Figure 3.

Paragraph beginning at line 20 of page 44, specifically lines 25 and 26, has been amended as follows:

A cDNA (Figure 1; SEQ ID NO:1) encoding a protein of 217 amino acids (Figure 2; SEQ ID NO:2) was identified as DSP-4. This sequence has significant homology to other MAP-kinase phosphatases (Figure 3). The identified cDNA contains the 651 base pair coding region, as well as associated 5' and 3' untranslated sequences. The active site domain for DSP-4 was localized to the region that ~~encoded by nucleotides beginning~~ begins at position 148 of SEQ ID NO:~~1~~2.

In the Claims:

Claims 3-5 have been canceled.

Claims 2, 6, 8, 10, 11, 12, 14 and 22 have been amended, and new claims 50-52 added, as follows:

2. (Amended) An isolated polynucleotide that encodes ~~at least ten consecutive amino acids of~~ a polypeptide ~~having a~~ comprising the sequence ~~corresponding to~~ as set forth in SEQ ID NO:2.

3. (Canceled) An isolated polynucleotide that encodes at least fifteen consecutive amino acids of a polypeptide having a sequence corresponding to SEQ ID NO:2.

4. (Canceled) An expression vector comprising a polynucleotide according to claim 2 or 3.

5. (Canceled) A host cell transformed or transfected with an expression vector according to claim 4.

6. (Amended) An isolated polynucleotide that encodes a polypeptide variant of the polypeptide comprising the sequence of SEQ ID NO:2, wherein the variant differs in one or more amino acid deletions, additions, insertions or substitutions at no more than 25% of the residues in SEQ ID NO:2, such that the polypeptide variant retains the ability to dephosphorylate an activated MAP-kinase ~~according to claim 1~~.

7. A polynucleotide according to claim 6, comprising the sequence in SEQ ID NO:1.

8. (Amended) An expression vector comprising a polynucleotide according to either claim 2 or claim 6.

9. A host cell transformed or transfected with an expression vector according to claim 8.

10. (Amended) An antisense polynucleotide comprising ~~at least 15 consecutive nucleotides complementary to~~ a polynucleotide that is complementary to a polynucleotide according to any one of claims 2, 6, 7, 11, and 50-52.

11. (Amended) An isolated polynucleotide that detectably hybridizes to the complement of the sequence ~~recited in~~of SEQ ID NO:1 under conditions that include a wash in 0.1X SSC and 0.1% SDS at 50 °C for 15 minutes, wherein said isolated polynucleotide exhibits at least 80% nucleotide identity to the polynucleotide comprising the sequence of SEQ ID NO:1.

12. (Amended) An expression vector comprising a polynucleotide according to any one of claims 10, ~~or claim~~ 11 and 50-52.

13. A host cell transformed or transfected with an expression vector according to claim 12.

14. (Amended) A method of producing a dual specificity phosphatase-4 (DSP-4) polypeptide, comprising the steps of:

(a) culturing a host cell according to claim 9 under conditions that permit expression of the DSP-4 polypeptide; and

(b) isolating DSP-4 polypeptide from the host cell culture.

22. (Amended) A method for detecting dual specificity phosphatase-4 (DSP-4) expression in a sample, comprising:

(a) contacting a sample with an antisense polynucleotide according to claim 10~~ or claim 11~~; and

(b) detecting in the sample an amount of DSP-4 polynucleotide that hybridizes to the antisense polynucleotide, and therefrom detecting DSP-4 expression in the sample.

23. A method according to claim 22, wherein the amount of DSP-4 polynucleotide that hybridizes to the antisense polynucleotide is determined using polymerase chain reaction.

24. A method according to claim 22, wherein the amount of DSP-4 polynucleotide that hybridizes to the antisense polynucleotide is determined using a hybridization assay.

25. A method according to claim 22, wherein the sample comprises an RNA or cDNA preparation.

50. (New) An isolated polynucleotide that encodes a polypeptide capable of dephosphorylating an activated MAP-kinase, said polynucleotide comprising a sequence at least 80% identical to a polynucleotide that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2.

51. (New) An isolated polynucleotide that encodes a polypeptide capable of dephosphorylating an activated MAP-kinase, said polynucleotide comprising a sequence at least 90% identical to a polynucleotide that encodes a polypeptide comprising the amino acid sequence of SEQ ID NO:2.

52. (New) The isolated polynucleotide of either claim 50 or claim 51, wherein the polypeptide that is capable of dephosphorylating an activated MAP-kinase comprises aspartic acid at position 119 of SEQ ID NO:2 and VHCNAGVSRAAAIV (SEQ ID NO:3) at positions 148 through 161 of SEQ ID NO:2.